Cardiovascular Frailty - making the shift towards customized care

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2020

document version
Publisher's PDF, also known as Version of record

Chapter 8

Summary and General discussion

The aim of this thesis was to cover three research areas on cardiovascular frailty: indicators of cardiovascular frailty, current management strategies, and treatment recommendations. Part 1 describes whether patients with cardiovascular disease (CVD) are at risk of becoming frail at a later moment in time, or whether frailty precedes CVD. It also shows the relation between types of orthostatic hypotension, cognitive decline and incident dementia. Part 2 outlines differences in cardiovascular risk management (CVRM) between non-frail and frail older adults in current clinical practice. Next, it highlights a clinical dilemma when treating hypertension in (older) patients with a high cardiovascular burden. Part 3 explains the value of a multidomain approach in heart failure, and provides suggestions for managing hypercholesterolemia in fit versus frail older adults. The current chapter summarizes the main findings from chapters 2 to 7, discusses methodological issues, and puts these findings in the context of current literature. Finally, we will provide implications for clinical practice and directions for future research.

Main findings

Part 1 Cardiovascular Frailty

Cross-sectional studies in community-dwelling older adults have demonstrated that patients with CVD are more likely to be frail than those without CVD [1-3]. However, these cross-sectional studies do not clarify whether CVD leads to frailty or whether frailty precedes the development of CVD. Thus, the question explaining the direction of this association remains to be answered. In **Chapter 2** we examined the cross-sectional and longitudinal bidirectional relation between CVD and frailty. For this, we used data from the Longitudinal Aging Study Amsterdam (LASA) in 1,432 older adults aged 65 years and over, who were followed for 17 years. In conclusion, the results show that older adults with CVD, especially those with heart failure, have an increased risk of being frail and/or becoming frail in the future. This association does not hold true the other way around, i.e. frailty does not precede development of CVD. Existing literature recognizes that patients with CVD, those with heart failure in particular, are more likely to be frail [3-7]. Longitudinal evidence however is not as abundant [8]. We added to the results from previous studies because we studied a broader range of specific CVDs. Also, our study had a longer follow-up period. Based on our results, it could be suggested that management of heart failure should shift from a merely 'cure-based' approach to a more 'care-based' approach. In the latter, outcomes relevant for older patients, such as quality of life and independence of care should be the main focus. Overtreatment and inappropriate polypharmacy should be avoided.

In **Chapter 3** we assessed the prevalence of early orthostatic hypotension (OH) and delayed and/or prolonged OH (as a marker of cardiovascular frailty) in subjects with subjective cognitive disease (SCD), mild cognitive impairment (MCI) and dementia. Next, we investigated the longitudinal association between these types of OH and clinical progression to either MCI or dementia. For

this, we used data from 1,882 participants with SCD, MCI or dementia from the Amsterdam Dementia Cohort [9]. The prevalence of OH increased across the spectrum of SCD (19%) to MCI (28%) and dementia (41%). This is in line with previous studies performed in the general population [10, 11]. Patients with vascular dementia and Lewy body dementia were most likely to have OH. In initially non-demented individuals, having delayed and/or prolonged OH at baseline was associated with an increased risk of clinical progression to MCI or dementia. This type of OH is more likely related to autonomic dysfunction and longer periods of cerebral hypoperfusion. Earlier studies have already shown that other autonomic dysfunction related (postural) blood pressure changes are associated with cognitive deterioration and incident dementia [12-15]. However, to our best knowledge, this was the first study focusing on differences in types of OH and clinical progression of cognitive disease. The results from our study point out that early OH can be seen as a benign and brief drop in blood pressure, but delayed and/or prolonged OH should not.

Part 2 Current Practice

CVRM guidelines state almost every older adult is eligible for a lipid-lowering drug. However, life expectancy, frailty or comorbidities may influence such treatment decisions. **Chapter 4** assesses the latter by giving a description of how many Dutch older adults, according to age, frailty, and comorbidities are prescribed a lipid-lowering drug. Using the Nivel Primary Care Database (Nivel-PCD), we were able to include data from 244,328 adults aged 70 years and older. In older adults with pre-existing CVD (n=55,309), 69% were prescribed a lipid-lowering drug. In older adults without CVD (n=189,019), this percentage was 36%. As previously reported [16], age was inversely associated with the number of lipid-lowering drug prescriptions. We hypothesized that frail older adults were less likely to be prescribed a lipid-lowering drug, due to a lower likelihood of benefits and a greater susceptibility to harms compared to fit older adults. However, in each age group, frail older adults and those with the highest number of chronic diseases, were most likely to be prescribed lipid-lowering therapy. This was the case for older adults with, as well as for older adults without pre-existing CVD. In conclusion, we demonstrated that general practitioners are less likely to initiate and/or more likely to discontinue lipid-lowering therapy with increasing age. However, contrary to our expectations, we also observed that frail older adults were most likely to be prescribed a lipid-lowering drug, and are therefore potentially overtreated. **Chapter 5** illustrates the same may also be true in terms of blood pressure lowering treatment. The 2018 European Society of Cardiology (ESC) hypertension guideline advises more intensive blood pressure (BP) management compared to previous editions [17]. Potential harm of low diastolic blood pressure (DBP) may therefore become of greater concern, a clinical dilemma recognized by a growing body of evidence [18, 19]. Hypertension guidelines advocate titrating BP according to SBP, based on office BP measurements. The occurrence of low DBP may therefore be greater than is to be expected based on office BP alone. Therefore, the study in Chapter 5 assessed how

many patients treated for hypertension have low DBP in office and during ambulatory blood pressure monitoring (ABPM). For this retrospective cross-sectional study, we obtained data from 848 patients treated for hypertension in whom an ABPM was performed at the outward clinic for internal medicine of Amsterdam UMC, location VUmc. Low office DBP was present in 10% patients, while 22% patients had low ambulatory DBP. We believe our data demonstrate the added value of ABPM to prevent potential overtreatment of (D)BP, as 1 out of 6 patients treated for hypertension with normal-to high office DBP, especially older adults with (cardiovascular) comorbidities, have low DBP during ABPM. Existing data on low DBP are mainly of observational origin, and merit confirmation with prospective trials. At least until then it remains questionable whether the benefits of lowering SBP outweigh potential negative effects of low DBP. However, given that the largest part of the patients with low DBP are older patients, and have more (cardiovascular) comorbidities, they are at higher risk of experiencing harmful effects of low DBP.

Part 3 Suggestions for Treatment

Major heart failure guidelines recognize that frailty impacts prognosis and treatment success, and therefore recommend screening for frailty [20]. Yet, the focus is laid on physical frailty (e.g. walking speed, Fried frailty criteria), and does not incorporate other common domains [8, 21-23]. In **Chapter 6** we studied whether having impairments in multiple domains is associated with 3-month and 6-month adverse outcomes (emergency department visits, hospital admissions and/or death). The results of this study suggest that having limitations in multiple domains is highly prevalent in older patients with heart failure. Next, we showed that the number of domains affected is more strongly associated with future adverse health outcomes than severity of heart failure and physical frailty. This was independent of relevant confounders. Our observations suggest the potential added value of a multidomain assessment approach in older heart failure patients. We believe that a multidomain assessment approach may aid clinicians to implement targeted intervention strategies. Lastly, having multiple domains affected may suggest management of these older heart failure patients should shift from a 'cure based' to a 'supportive care based' treatment strategy.

The number of older adults with (risk factors for) CVD is increasing. Thus, the sum of older adults potentially eligible for lipid lowering drugs will increase as well. This has risen questions about the benefits and harms of lipid-lowering therapy in older adults with a varying number of (cardiovascular) comorbidities and differing functional status. Current CVRM guidelines however are solely based on data from clinical trials in relatively young and fit adults [24, 25]. They are single-disease based, and give advice on how to treat 'average' patients. Translating these recommendations to older adults may therefore be inappropriate. This knowledge gap is addressed in the recently published Dutch addendum 'CVRM in (frail) older adults' [26]. In line with this addendum, **Chapter 7** discusses important differences in managing hypercholesterolemia between young and older adults. We provide an overview of the current literature on lipid-lowering

drugs in older adults, and explain why heterogeneity of cardiovascular risk increases with age. We set out why and how we think estimated 10-year risk of CVD needs to be put into the perspective of a patient's estimated life expectancy when deciding on whether or not to prescribe lipid-lowering therapy. We suggest treatment decisions for hypercholesterolemia in adults aged 75 years and over should shift from a strictly 10-year cardiovascular risk driven approach to a patient-centered and lifetime benefit-based approach. Finally, we provide recommendations on how to implement this in daily clinical practice by giving advice on when to initiate, continue and deprescribe lipid-lowering drugs in fit and frail adults aged 75 years and over.

Future perspectives

Recommendations for clinical practice

Multidomain approach

Due to the expanding number of older adults, health care providers will be increasingly faced with a growing population of frail older adults [27]. Frail older adults are at increased risk of adverse health outcomes, such as falls, hospitalization and mortality [28, 29]. Hence, the 2016 European Society of Cardiology (ESC) guideline for management of heart failure recommends screening for frailty [20]. However, focus is laid on physical frailty instead of a multidomain approach. In this thesis we concluded that a multidomain approach adjusted to level of frailty is not yet common practice in daily clinical care. This was illustrated in **Chapter 4**. Although prescriptions for lipid-lowering medication decreased with age in older adults, within each age group, frailty was positively associated with number of lipid-lowering drugs prescriptions. **Chapter 6** illustrates that having impairments in multiple geriatric domains is more strongly associated with adverse health outcomes than physical frailty alone or heart failure severity. Thus, compared to focusing on the concept of frailty, a multidomain approach is of added value in identifying patients at risk of adverse health outcomes. Having impairments in multiple domains may signal the need for a transition from a merely 'cure-based' strategy to a more 'care-based' treatment strategy. In the latter, patient-relevant outcomes such as quality of life and independency of care become of increasing importance, rather than achieving full recovery and prolonging life [25, 30]. Unnecessary treatment with cardio protective drugs (i.e. 'overtreatment') must be avoided, because their harmful effects may disproportionally affect these frail older adults. For patients with mild cognitive and/or physical impairments there may lay possibilities in (cardiac) rehabilitation programs aiming to improve and/or stabilize functional status. In patients with fewer options for recovery, advanced care planning should play a more prominent role. Regularly assessing whether previously initiated interventions should be continued, adapted or discontinued is herewith pertinent. Determining the most optimal moment to have conversations on goals-of-care is difficult, but should preferentially take place in an outpatient setting [31]. It provides a

moment to evaluate patient' values and future care preferences [32]. A setting in which the results of a multidomain screening are discussed may provide opportunities to introduce such conversations. After all, having impairments in multiple domains signals a patient's deteriorating health.

We believe a multidomain approach should be routinely incorporated in the complex clinical care for older adults. A first step to do so may lay in establishing a common awareness among healthcare providers on the concept of frailty and the additional value of a multidomain approach. This may help change physicians' perspectives on how to apply one-dimensional guidelines to their multidimensional older patient. Most physicians work in the cure-setting of medicine, and are not well enough equipped – in terms of training, as well as in terms of time – to incorporate such a geriatric and multidisciplinary mindset into their day-to-day work. Thus, there lay opportunities and challenges in handing physicians working in non-geriatric specialties tools with which to assess, manage and integrate frailty and a multidomain approach into the daily clinical care of their older patients. With this, patient-centered care at the right time, the right place, in the right setting of care is provided. In order to do so, merit may be found in a recently introduced approach for frailty referred to as 'resilience' [33]. The added value of this concept is that resilience reflects a dynamical view on a patient's ability to recover, while frailty provides a more static view on a patient's functional capacity [33], see below.

Guidelines

Guidelines are currently one-disease based, solely based on data from clinical trials in relatively young and fit adults and give advice on how to treat 'average' patients [24, 25]. This makes it challenging to apply them to older adults with multiple diseases and deteriorated functional capacity [25]. Also, they do not always align with an individual patient's goals of care, because adhering to the guidelines may negatively influence physical or cognitive functioning (e.g. due to side effects of medication) [28, 29, 34, 35]. Ideally, guidelines should represent older patients on the continuum from fit to frail. However, it remains a challenge to translate the dynamical concept of frailty into the static concept of a guideline. Incorporating frailty into guidelines has gained momentum, but, as described above, these guidelines tend to focus on physical frailty, while cure and care in older adults calls for a broader approach of geriatric syndromes.

Over the past years, deprescribing (cardio protective) drugs to prevent unnecessary polypharmacy has gained more attention [36-38]. In the Netherlands for example, a national deprescribing guideline is being developed [39]. Deprescribing cardio protective drugs is one of the main items. Current Cardiovascular risk management (CVRM) guidelines however, do not – or only very limitedly – address when to consider deprescribing cardio protective drugs. This is partially because prospective randomized studies on deprescribing lipid lowering therapy in older adults are scarce, making deprescribing seem progressive. However, particularly in frail older adults, negative effects of treatment (e.g. side effects, drug-drug interactions) may outweigh potential

benefits in terms over preventing cardiovascular diseases (CVD) (**Chapter 7**). In line with the Dutch addendum 'CVRM in (frail) older adults' [40], articulating recommendations on when to deprescribe treatment in new CVRM guidelines offers the prospects of optimizing treatment for the individual older patient. However, all of the above being said, we reckon – even if guidelines are broadly formulated – we need to realize that they will never be applicable to every single older patient. Deliberately deviating from guidelines will therefore still be essential to provide patient-centered care for each individual patient.

Resilience

Frailty represents a patient's ability to tolerate treatment, and to what degree a certain stressor (e.g. surgery, cardiovascular event) may affect health and functional status [29]. In some patients, CVD cause a significant loss in (physical, cognitive) functioning, and a reduction in tolerance to treatment. However, other patients with CVD have the ability to recuperate and do not experience (permanent) disabilities. A growing number of researchers in the field of geriatric medicine are referring to this potential to recuperate as 'resilience' [33]. The added value of this relatively new approach to frailty is that resilience reflects a dynamical view on a patient's ability to recover, while frailty provides a more static view on a patient's functional capacity. It is proposed that certain physiological stimulus-response tests can be used to identify in which patients a stressor will lead to deterioration (i.e. not resilient), and which patients are likely to recover (i.e. resilient) [33]. The following markers have been previously proposed and can be seen as examples, as they are associated with frailty and mortality: slow heart rate recovery after treadmill, impaired SBP recovery in the first minute after standing, and longer recovery times of glucose levels after a high glucose challenge [40-43]. Based on the results of this thesis, we provide two additional examples of possible 'resilience markers'. The first is delayed and/or prolonged orthostatic hypotension, and the second low DBP. **Chapter 3** describes having delayed and/or prolonged OH was associated with an increased risk of dementia, while early OH was not. In other words, patients with the 'frailer' blood pressure regulation system who were not able to quickly recover from the orthostatic blood pressure drop (i.e. those with less resilience) were more likely to experience negative cognitive outcomes at a later point in time. **Chapter 5** describes our second potential marker of resilience. Compared with patients with normal-to-high DBP (>70 mmHg), patients with low DBP (≤70 mmHg) were older, had more comorbidities, took more (antihypertensive) drugs, and were more likely to have (risk factors for) CVD. As these patients are also the ones most prone to experience potential negative effects of low DBP [44, 45], having low DBP may be another indicator of a less resilient blood pressure regulation system. The clinical relevance of these resilience markers has yet to be examined prospectively. However, they may have the potential to distinguish patients with low ability to recuperate after disease from patients with a greater likelihood of recovery. Accordingly, additional care or treatment may be provided in order to personalize a patient's disease management.

Methodological considerations

Generalizability

This thesis describes several studies on cardiovascular frailty in older adults. We used data from different cohort studies from various settings and designs, ranging from large longitudinal community-based samples to prospective data from patients visiting an outpatient clinical in a general and academic hospital. We believe this approach enabled us to get a broad picture of cardiovascular frailty in primary, secondary and tertiary care. However, certain limitations in terms of generalizability warrant discussion. Some of the sample sizes of our studies were considerable. Particularly the study using data from the Nivel-PCD (**Chapter 4**) with data on 244,000 adults aged ≥70 years reports a very large sample size. However, in other studies certain subgroups were small. For example, of all 848 patients included in the study described in **Chapter 5**, 10% of the patients had low DBP in office and 22% during ambulatory blood pressure monitoring. Dividing these patient groups according to age led to small subgroups. Small subgroups were also observed in the study assessing the value of a multidomain geriatric assessment in 197 older patients with heart failure (**Chapter 6**). The absolute number of patients experiencing adverse health events per subgroup (e.g. heart failure severity, level of frailty and number of domains affected) was small. These small numbers are reflected in the large confidence intervals presented in table 2. Small subgroups may have also lead to over-adjustment of our models in this study.

Observational studies and risk of bias

Confounding and selection bias

The most important limitation that needs to be considered in all studies including participants at high ages, and thus all studies described in this thesis, is the role of survival bias and selection bias. Patients with the highest level of frailty, e.g. those with many comorbidities and/or functional impairments, are least likely to participate in research. During study follow-up, particularly the frailest participants are likely to drop out. This leads to a selection of relatively healthy older adults. This must be kept in mind when generalizing the results to the population described in the study. The study described in **Chapter 5** provides an example of selection bias. The data for this study were suitable to answer our research question. However, they were collected for clinical care purposes and not specifically for the purpose of our study. Hence, proper randomization was not achieved, thereby ensuring that our study population is not necessarily representative of the population intended to generalize the study results to. Also, the ABPM was performed in patients visiting an academic medical center, and presumably only patients in whom the results of the ABPM would have therapeutic consequences. Generalizing the results to populations in e.g. primary care and/or very frail older adults must therefore be done with caution. **Chapter 2, 3** and **6** describe longitudinal/ prospective studies. As with all such study designs, particularly studies performed in older adults, (selective) drop-out of participants is inevitable. To assess whether the

drop-out of participants may have influenced the results of these studies, we performed secondary analyses assessing whether the baseline characteristics of participants who were lost to follow-up were statistically different from those not lost to follow-up. In these studies, statistically significant differences between participants lost to follow-up and those included in the analyses were not likely to influence our results. Yet, we are not able to fully rule out the possibility of selection and/ or survival bias.

Another form of bias worth mentioning in this thesis is confounding by indication. Confounding by indication is likely to happen when use of a particular drug is linked to the outcome of interest in a study. **Chapter 4** provides an example in this thesis. In this study we observed that frail older adults were more likely to be prescribed a lipid lowering drug compared to fit older adults. An explanation for this could be the higher number of primary care visits in frail older adults compared to less frail older adults. Frail older adults are therefore better monitored by their general practitioner and thus more likely to be diagnosed with the diseases/ symptoms included in the frailty index we used in this study (Drubbel frailty index). Additionally, the higher number of primary care visits also increase the likelihood of being prescribed a lipid lowering drug. In other words, being prescribed a lipid lowering drug may be confounded by the indication frailty.

Lastly, we would like to discuss a form of bias applicable to all the studies included in this thesis; the possibility of residual confounding. We adjusted all our models for potential confounders. However, even after doing so, there remain factors in the design and/or analysis of a study distorting the results. An example of this is present in **Chapter 2** and **6**. Our secondary models were adjusted for age, sex, and several comorbidities. It is likely that there were additional confounding factors we did not consider. Also, especially in **Chapter 6**, the total number of patients included in the analyses were too small to fully adjust our models in a statistically correct manner.

Reversed causality

Longitudinal studies are subject to the possibility of reverse causality (i.e. instead of X causing a change in Y, Y is causing changes in X). The association studied in **Chapter 2** of this thesis provides an example of this. Using data from the Longitudinal Aging Study Amsterdam, we observed that having CVD precedes frailty. Analyses studying the reverse association revealed that in this older population frailty does not precede development of CVD. Although we performed time-lag analyses to minimize the possibility of reserve causality, we cannot rule out that frailty may lead to an increased risk of CVD. After all, physical inactivity and its sequelae (e.g. obesity) due to frailty may be a risk factor for development of CVD. The study in **Chapter 3** described a second relationship with the possibility of reverse causality. The results of this study suggest prolonged and/or delayed orthostatic hypotension is associated with an increased risk of clinical progression to mild cognitive impairment and/or dementia. However, the reserve association may also hold true; neurodegeneration in patients with dementia may lead to systemic autonomic failure and

subsequently to orthostatic hypotension. Another possibility is that orthostatic hypotension and cognitive disabilities can both be seen as an indicator of neurodegenerative disease instead of a orthostatic hypotension being a risk factor for neurodegenerative disease. Unfortunately, due to a short period of follow-up (2.2 years) and lack of data on blood pressure during follow-up, we were not able to perform time-lag analyses to minimize the possibility of reverse causality.

Competing risk

Another bias in longitudinal research specific for survival analyses (e.g. Cox-regression) is the effect of competing risk by mortality. A competing risk is an event that either hinders the observation of the event of interest or modifies the chance that this event occurs [46]. For example, in **Chapter 2**, death is an event that competes with the event studied, i.e. frailty. This leads to an overestimation of the effect of CVD on becoming frail. With Cox-regression analyses, patients who die or are lost to follow-up are censored. Censored individuals are still considered at risk of becoming frail. Naturally, this is impossible for deceased patients leading to an overestimation of the risk of becoming frail. Unfortunately, we were unable to apply alternative methods specifically designed for analysing competing risks data.

Besides the pitfalls of observational studies, we believe these study designs are essential for research in older adults. After all, randomized controlled trials (RCTs), study designs considered to be the holy grail of scientific medical evidence, are difficult to conduct in (frail) older adults (see below).

Future research

The concept of frailty is increasingly being introduced in clinical care and guidelines. However, the translation from research to daily clinical practice remains complicated [27]. An important reason for this is the lack of a universal definition of (cardiovascular) frailty, and thus tools to objectively assess it [27]. This debate aside, there is need for more clear-cut evidence that can guide physicians on how to anticipate potential benefits of treatment in (frail) older adults, while at the same time avoiding potential harms. As described previously, frailty should be seen as a continuum instead of as a dichotomous entity [47]. Based on subjective impressions, extremely fit patients and extremely frail patients are easily recognized by (non)physicians. However, a large grey area between these two extremes exist. Objective markers differentiating between patients who benefit and patients in whom negative effects outweigh harms, and what the value of these markers is in terms of clinical decision making remain to be discovered. We suggest three research strategies to tackle this issue: 1) including frail older adults in research, 2) rely on other research designs than solely randomized clinical trials (RCTs), and 3) use outcomes relevant for older patients (e.g. quality of life) instead of traditional 'hard' outcomes such as cardiovascular events and death.

1. Including (frail) older adults in research

Clinical trials and the patients participating in them are key to advance our knowledge on how to treat older adults across the entire spectrum of fit to frail. Thus, in order to justify standard practice for patients of all ages, a crucial initial step is to include older adults representative of the broad population of older adults in (clinical) trials. Unfortunately, a mismatch in age and level of comorbidities between trial participants and the clinical patient population is still common [48]. Numerous barriers to successfully conducting trials in (frail) older adults exist. For example, functional impairments make it more difficult to adhere to intricate trial regimes, and cognitive impairments can make getting informed consent for study participation complex. Drop-out rates are generally higher compared to trials performed in younger patients. Furthermore, the large heterogeneity in study participants can create issues concerning drawing unambiguous conclusions of the results. However, as demonstrated previously, RCTs in frail older adults are possible. The Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) trial for example successfully included 385 participants aged ≥75 years with mild cognitive deficits, and randomized these patients to continuing versus discontinuing antihypertensive drugs [49]. Despite this relatively frail population of older adults, the drop-out rate was limited to 7.5%, which was mainly due to withdraw of informed consent. Notwithstanding, clinical trials will always have trouble including the frailest patients. Thus, for these patients we propose to also focus on other research designs.

2. Going beyond randomized controlled clinical trials

RCTs are considered the holy grail of scientific medical evidence. However, as described above, conducting RCTs in frail older adults is difficult. We therefore call upon all stakeholders in the field of geriatric research (e.g. policy makers, geriatricians, patient expert panels, guideline and grant committees) to stimulate a discussion on other research designs/strategies than the classical RCT to advance the field. The recently published Netherlands Organization for Health Research and Development Netherlands (ZonMW) report 'Older Adults in the Hospital' provides initial suggestions for this [24]. The authors promote before-after designs, mixed-methods designs, stepped wedge-studies, prospective cohort studies, deprescribing trials, and pragmatic clinical trials in which the efficacy of (complex) interventions already performed in daily clinical practice are studied. Clinical trials which build upon current infrastructures that already exists for clinical care will increase the chance of completion. This also holds true for expanding pilot projects that have been successfully run in a small setting. Lastly, we would like to mention the relevance of observational cohort studies performed in a clinical patient setting. Many argue that observational cohort studies provide insufficient scientific evidence to change of clinical practice, because they are subjective to several types of bias, have not always adequately accounted for confounding or reverse causality, and are mainly performed in community-based populations. However, these studies are able to include a large number of patients who are likely to be too frail to participate

in intervention trials (e.g. patients included in the Amsterdam Dementia Cohort (**Chapter 3**), and at the outpatient heart failure clinic (**Chapter 6**)). As mentioned above, chances of successful inclusion are increased when these cohorts are built upon infrastructures that already exist for clinical care.

Although deprescribing cardio protective drugs has gained significant interest over the past few years [50, 51], results from our study in **Chapter 4** suggest physicians are still reluctant when it comes to discontinuing CVRM medication. An important explanation for this is lack of prospective randomized studies assessing the positive, and negative effects of deprescribing these drugs. The relevance of deprescribing trials with cardio protective drugs was not only articulated by the previously mentioned ZonMW report, but also by the Dutch Society for Clinical Geriatrics (NVKG). Identification of the harm-benefit balance of (initiating and discontinuing) cardio protective drugs, including statins and antihypertensive drugs, in frail elderly are top priorities (number 1 and 2 out of 10) on their research agenda [52]. Also, in a recent review on the role of statins in older adults without CVD, experts state that perhaps "only deprescribing studies could confirm the question about benefits of continuing earlier started treatment in old age" [51]. In terms of deprescribing lipid lowering therapy, a recent retrospective observational study suggested an increased risk of cardiovascular events after deprescribing statins in older patients [53]. However, randomized deprescribing trials in patients with advanced disease observed no increase in mortality after deprescribing statins, and potentially improved quality of life [54, 55]. We express optimism about an ongoing statin deprescribing trial in France, Statins In The Elderly (SITE, NCT02547883), which is recruiting 2,430 participants aged ≥75 years treated for primary prevention. The study outcomes do not only include mortality and cardiovascular events, but also quality of life. Results from deprescribing trials may inform guideline committees and physicians on whether, and if so, for which patients, more restraint towards cardio protective drug prescriptions is appropriate.

3. Translation to outcomes relevant for older patients

With increasing age, and increasing level of frailty, outcomes such as quality of life, functional capacity, and independence of care become more and more important goals of care for older patients [24, 25]. However, traditional RCTs, also in older adults, currently still have 'hard' endpoints, such as cardiovascular events and death, as their primary endpoint. Applying the results of these 'hard endpoint' studies to older patients may therefore not necessarily mean that they will benefit from the studied intervention [56]. In fact, the intervention may potentially even cause harm, because it negatively influences functional status (i.e. due to side effects, drug-drug interactions), and quality of life [28, 29, 34, 35]. In our opinion, we suggest future research in older adults should focus on outcomes more appropriate for older adults, such as quality of life, enhanced symptom control or functional status.

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